Hot Topics in Adult Infectious Diseases 2014

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Inclusion Criteria
- Appeared in a high impact medical journal 2013 – 2014
- Likely relevant to ID clinical practice

Exclusion Criteria
- Covered by a previous years’ presenter at this session
- Topic to be covered in more detail at this conference:
  - MERS
  - Various Bird Flus

And time constraints...
Topics Covered

1. Hepatitis C

2. Two Papers with Direct Application to ID Practice
   a. Penicillin for Recurrent lower extremity Soft Tissue Infection
   b. Predicting who will develop chronic HBV

3. Two Tests that Might Improve Antimicrobial utilization:
   a. MALDI-TOF
   b. Aspergillus Galactomannan /PCR

4. Developments in HIV
   a. New opportunistic pathogen: *Emmonsia pasteuriana*
   b. Dolutegravir
   c. Where is the HIV Field Headed?
Rationale of Antiviral Therapy for HCV

- Prevent hepatic decompensation, HCC, death
- Prevent need for transplantation
- ?Improve histology?
Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study


Suppression of HBV DNA Impact on Liver Histology
(Same for HCV?)

- Cohort of n=641 patients originally enrolled on tenofovir or adefovir trial for eAg+/- HBV
- After initial 48 weeks, open label ongoing tenofovir for n=348 who agreed to repeat liver biopsy at week 240
- All patients (with or without cirrhosis at baseline) had undetectable HBV DNA at 5 year
CRTC demands more Canadian content in adult movies.

Oh yes! yes! yes!... EH?
Hepatitis C: Direct Acting Antiviral Agents (DAA)
(In Yellow: Agents available for use in Canada)

**Translation and polyprotein processing**
- **NS3/4 protease inhibitors**
  - Boceprevir,
  - Telaprevir,
  - Simeprevir,
  - Faldaprevir,
  - ABT-450

**Transport and release**

**Fusion and uncoating**

**(+)** RNA

**Membranous web**

**NS5B polymerase inhibitor**
- Inhibitor Chain Terminators
  - Nucleos(t)ide
    - Sofosbuvir,
    - Doleobuvir,
    - ABT-333
  - Non-nucleoside

**NS5A inhibitors**
- Daclatasvir,
- Ledipasvir

**Replication and assembly**

Evolution of Interferon-Based HCV Therapies 2013 - 2014

- Improving SVR rates
- Decreasing duration of therapy to 12 weeks
- Still use only one DAA

DAA Component
- Increasing potency
- Decreasing pill burden
- Better adverse effect profile
- Fewer drug interactions
- More than genotype 1a/1b
Peg-IFN Based Regimens Available for GT1 - Overall SVR Rates

Higher SVR

- GT 2 /3
- F0 – F2
- IL28B CC

Lower SVR

- GT 1a/1b
- F3 or cirrhosis
- High VL
- IL28B non CC

Historic Predictors of SVR with PEG –IFN Based Regimens

- Treatment-experienced partial /null responders have lower SVR than treatment-naïve patients
- Lower SVR rates for HIV/HCV coinfection
- These predictors will be increasingly obsolete in the era of DAAs
Improving SVR for F3/F4 with PEG-IFN Based Regimens for Patients

Evolution to All-Oral HCV Therapies

- Timing of drug approvals uncertain
- Cost and reimbursement will be key considerations

IFN-Free, Maintain RBV

- Abbvie Trials with ABT-450/r and ABT-333 and/or ABT 267

IFN-Free, RBV Free

- SOF/Ledipasvir +/- RBV
  - LONESTAR Trial
- SOF/Daclatasvir +/- RBV
  - A1444040 Trial
- Faldaprevir/Doleobuvir +/- RBV
Phase 2b Trial of Interferon-free Therapy for Hepatitis C Virus Genotype 1

Kris V. Kowdley, M.D., Eric Lawitz, M.D., Fred Poordad, M.D., Daniel E. Cohen, M.D., David R. Nelson, M.D., Stefan Zeuzem, M.D., Gregory T. Everson, M.D., Paul Kwo, M.D., Graham R. Foster, F.C.R.P., Mark S. Sulkowski, M.D., Wgang Xie, Ph.D., Tami Pilot-Matias, Ph.D., George Lioissis, B.A., Lois Larsen, Ph.D., Amit Khatri, Ph.D., Thomas Podsadecki, M.D., and Barry Bernstein, M.D.

All Oral, IFN-free GT1

- Phase 2b trial – small numbers in each group
- Few treatment-naïve patients with advanced fibrosis
- All received RBV

- Various combinations of ABT-450/r (PI) with either or both of ABT 267 (NS5A), ABT 333 (NS5B)
- Treatment duration 8, 12 or 24 weeks
- Previously treated patients did better with at least 12 weeks of treatment
Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial

Eric Lawitz, Fred F. Poordad, Phillip S Pang, Robert H Hyland, Xiao Ding, Hongmei Mo, William T Symonds, John G McHutchison, Fernando E Membreno

- All-oral, IFN-free, GT1

- Open-label phase 2 trial, single tablet SOF/LDP pill
- Randomization 1:1:1 of 60 Rx-naïve non-cirrhotic patients to:
  a. 8 weeks SOF/LDP (NS5B + NS5A)
  b. 12 weeks SOF/LDP
  c. 8 weeks SOF/LDP/RBV
- Randomization 1:1 of 40 prior PI failures to:
  a. 12 weeks of SOF/LDP vs SOF/LDP/RBV
- Few AEs, mainly due to RBV
- Limitation of this study: n=100, and even fewer (n=20) with cirrhosis
All Oral, Interferon-free, GT1 – 3

- Open label study of n=167 GT1 patients with few cirrhosis cases
- Initial protocol with 1 weeks lead-in SOF removed subsequently
- Included n=44 prior virologic failures with telaprevir or boceprevir regimens
- Randomization to DCL/SOF +/- RBV for 24 weeks

RESULTS

Overall, 211 patients received treatment. Among patients with genotype 1 infection, 98% of 126 previously untreated patients and 98% of 41 patients who did not have a sustained virologic response with HCV protease inhibitors had a sustained virologic response at week 12 after the end of therapy. A total of 92% of 26 patients with geno-
Faldaprevir and Deleobuvir for HCV Genotype 1 Infection

Stefan Zeuzem, M.D., Vincent Soriano, M.D., Ph.D., Tarik Asselah, M.D., Ph.D., Jean-Pierre Bronowicki, M.D., Ph.D., Ansgar W. Lohse, M.D., Beat Müllhaupt, M.D., Marcus Schuchmann, M.D., Marc Bourlière, M.D., Maria Buti, M.D., Stuart K. Roberts, M.D., Ed J. Gane, M.D., Jerry O. Stern, M.D., Richard Vinisko, M.A., George Kukolj, Ph.D., John-Paul Gallivan, Ph.D., Wulf-Otto Böcher, M.D., and Federico J. Mensa, M.D.

All Oral, Interferon-free, GT1 Treatment- Naïve

- Phase 2b open label trial, n=362
- Approximately 10% with cirrhosis
- Multiple (5) arms with once daily FDV (PI) and varying deleobuvir (NS5B) and RBV doses
- Less impressive SVR than NS5B / NS5A combinations

| Table 2. Virologic Response during and after the Treatment Period. |
|-------------------------|-------------------|-------------------|------------------|------------------|
| Variable                | TID16W (N = 81)   | TID28W (N = 80)   | TID40W (N = 77)  | BID28W (N = 76)  |
|                         | number/total number (percent) | number/total number (percent) | number/total number (percent) | number/total number (percent) |
| Undetectable HCV RNA 12 wk after completion of therapy: sustained virologic response |
| All patients            | 48/81 (59)        | 47/80 (59)        | 40/77 (52)       | 54/78 (69)       |
| Patients with genotype 1a | 13/34 (38)       | 14/32 (44)        | 16/34 (47)       | 13/30 (43)       |
| Patients with genotype 1b | 35/47 (74)       | 33/48 (69)        | 24/43 (56)       | 41/48 (85)       |
| Patients with IL28B CC  | 14/21 (67)       | 14/21 (67)        | 12/19 (63)       | 16/19 (84)       |
| Patients with IL28B non-CC | 34/60 (57)      | 32/58 (55)        | 28/58 (48)       | 38/59 (64)       |
|                         | 11/33 (33)       |
Can We Cure All Hepatitis C Patients?

- Need more subgroup data (post-Tx, cirrhosis, HIV-HCV coinfection, different genotype, Black ancestry)
- Will likely have many different ways to achieve virologic suppression in next five years
- For developing countries, will we see activism movements regarding access?

Over the past few years, new medicines for HCV infection have begun to transform the treatment landscape, and, just in the past few months alone, the development of new regimens has been so successful that disease experts are heralding an era where all patients can be cured, even debating whether eradication is possible.

Only just the beginning of the end of hepatitis C

2014 marks the 20th anniversary of the identification of the hepatitis C virus (HCV). HCV infection continues to be a major global health problem. Unlike many chronic diseases, hepatitis C can be cured, but it is difficult to treat, not all patients are responsive, side-effects can be severe, and progression to end-stage liver disease and liver cancer is common. Over the past few years, new medicines for HCV infection have begun to transform the treatment landscape, and, just in the past few months alone, the development of new regimens has been so successful that disease experts are heralding an era where all patients can be cured, even debating whether eradication is possible.

The main drawback of these new agents is the huge price tag, which will make treatment out of reach for people in the developed and developing world. Indeed, current treatment uptake is also impeded by cost. One 12 week course of sofosbuvir will cost US$84,000, even though the scientist involved in formulating sofosbuvir, Raymond Schinazi, estimates costs at just $1400. An even lower price was shown by Andrew Hill and colleagues in a recent study. Based on the fact that the new hepatitis C treatments are comparable in molecular structure and chemistry to HIV antiretrovirals, the authors used the same market dynamics to determine.
Penicillin to Prevent Recurrent Leg Cellulitis


- Direct advertising – hospital recruitment; dermatologist investigators
- Episode of cellulitis in the preceding six months were eligible with a prior episode in the last three years
- Randomized (DB) to penicillin 250mg po BID vs. placebo (n=136 vs. 138)
- Treatment adherence monitored by self-reporting an follow-up phone calls

Clinical Situation
47F, above ideal body weight, right leg cellulitis

- Last episode in 2011 in the same lower extremity
- No other underlying diseases
- No hardware, laceration or trauma preceding the cellulitis
- Responding to IV Cefazolin and ready for discharge

Should long term “suppressive” antibiotics be prescribed?
Table 1: Baseline Characteristics of the Study Participants.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Penicillin (N = 136)</th>
<th>Placebo (N = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting leg edema or ulceration associated with cellulitis — no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>45 (33)</td>
<td>44 (32)</td>
</tr>
<tr>
<td>Edema</td>
<td>81 (60)</td>
<td>82 (59)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Both</td>
<td>9 (7)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>58.1±12.6</td>
<td>57.4±14.4</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>59 (50–65)</td>
<td>58 (46–69)</td>
</tr>
<tr>
<td>Female sex — no. of patients (%)</td>
<td>83 (61)</td>
<td>82 (59)</td>
</tr>
<tr>
<td>White race and British nationality — no. of patients (%)</td>
<td>115 (85)</td>
<td>121 (88)</td>
</tr>
<tr>
<td>No. of previous cellulitis episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.7±4.3</td>
<td>3.8±4.8</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>2 (1–5)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Local warmth, tenderness, or acute pain — no. of patients (%)</td>
<td>136 (100)</td>
<td>138 (100)</td>
</tr>
<tr>
<td>Erythema at the affected site — no. of patients (%)</td>
<td>135 (99)</td>
<td>136 (99)</td>
</tr>
<tr>
<td>Edema at the affected site — no. of patients (%)</td>
<td>135 (99)</td>
<td>138 (100)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>35.1±9.4</td>
<td>35.2±9.5</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>33.7 (27.7–38.9)</td>
<td>32.5 (27.8–40.7)</td>
</tr>
<tr>
<td>Chronic edema — no. of patients (%) †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymmetric</td>
<td>64 (47)</td>
<td>64 (46)</td>
</tr>
<tr>
<td>Symmetric</td>
<td>28 (21)</td>
<td>28 (20)</td>
</tr>
<tr>
<td>Venous insufficiency — no. of patients (%)</td>
<td>36 (26)</td>
<td>34 (25)</td>
</tr>
<tr>
<td>Leg ulceration subsequent to cellulitis — no. of patients (%)</td>
<td>13 (10)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Tinea pedis or toe-web maceration — no. of patients (%)</td>
<td>52 (38)</td>
<td>48 (35)</td>
</tr>
<tr>
<td>Surgery &gt;2 wk before the index cellulitis episode — no. of patients (%)</td>
<td>22 (16)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Blunt injury — no. of patients (%)</td>
<td>6 (4)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Definite or possible onychomycosis — no. of patients (%)</td>
<td>30 (22)</td>
<td>39 (28)</td>
</tr>
<tr>
<td>Inpatient admission for index episode of cellulitis at baseline — no. of patients (%)</td>
<td>65 (48)</td>
<td>59 (43)</td>
</tr>
<tr>
<td>Duration of hospital stay for hospitalized patients — days</td>
<td>7.7±3.7</td>
<td>5.7±4.3</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. No significant between-group differences were observed at baseline. BMI denotes body-mass index, calculated as the weight in kilograms divided by the square of the height in meters.
† The values for chronic edema and leg ulceration at baseline vary slightly from the values for the stratification variables (preexisting leg edema or ulceration associated with cellulitis) as a result of the different data-collection methods used.
Results

Risk factors for prophylaxis failure during Year 1:

- BMI > 33
- Three or more prior episodes
- ?presence of edema
Clinical Situation: 42M, MSM with an acute febrile icteric due to acute HBV

- 159/215 Japanese patients with acute HBV between 1994 to 2010 followed for clinical outcomes (retrospective)
- no patients received antiviral therapy
- Quantitative HBsAg, HBV DNA, and genotype available on all
- Duration of HBsAg divided into:
  a. Group 1 (<3 mo)
  b. Group 2 (3 – 6 mo)
  c. Group 3 (6 – 12 mo)
  d. Group 4 (>12 mo)

Peak AST 400, ALT 700

Initial HBV DNA 2.81 E+9 IU/mL (1IU = 5.82 c/mL)

Will he develop Chronic Hepatitis B?
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a. Group 1 (<3 mo)
b. Group 2 (3 – 6 mo)
c. Group 3 (6 – 12 mo)
d. Group 4 (>12 mo)

Results

- 6% cleared HBsAg between six and twelve months (Group 3)
- 8 week HBV DNA >10E+6IU/mL at week 8 predictive of chronic (>12mo) infection
- 12 week quantitative HBsAg >1,000IU/mL (readily available in Canada?) predictive
Will MALDI-TOF Improve BSI Outcomes?

- Single centre pre–post intervention period during same three month calendar interval (Sept – Nov)
- Patients with BSI identified at admission / in-hospital
- During MALDI-TOF period, no direct testing on blood cultures
- Lab work hours 0600 – 2330h
- Multiple primary and secondary endpoints

Antibiotic Stewardship Team (AST): 2 IDs, 3 ID Pharms, 1 ID Pharm Resident

24/7 email notification to AST of +BC, updated ID, susceptibilities

Preintervention:
- No real time BC intervention except yeast on Gram Mo – Fri
- Restricted antimicrobial reviewed

Intervention:
- Real time BC interventions based on Gram, ID and susceptibilities using institution / evidence-based guidelines
- ?7d / week
Combined MALDI-TOF and AST Intervention: Results

- Outcome analysis on pre-intervention (n=256) and intervention period (n=245)
- Shorter time to effective therapy (30.1h vs. 20.4h)
- Shorter time to optimal therapy (90.3 vs. 47.3h)
- Significant de-escalation and discontinuation at time of organism identification

Table 4. Antimicrobial Stewardship Team Interventions

<table>
<thead>
<tr>
<th>Intervention Description</th>
<th>Timing of Intervention Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrowed coverage to target the isolated organism</td>
<td>Gram Stain</td>
</tr>
<tr>
<td>Discontinued therapy targeting organisms not isolated</td>
<td>5</td>
</tr>
<tr>
<td>Initiated or broadened coverage</td>
<td>39</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
</tbody>
</table>

Total (%) | 54 (25.7) | 75 (35.7) | 81 (38.6) | 210 (100)

Interventions accepted (%) | 49 (90.7) | 62 (82.7) | 78 (96.3) | 189 (90.0)
Impact of AST Intervention

Limitations:

- Improved time to effective therapy was mainly in response to the Gram stain, rather than organism ID
- Would real-time +BC ASP interventions achieve the same mortality endpoint
- Long term sustainability of ASP interventions?
Stewardship for Antifungal Therapy?

- High risk patient population undergoing chemotherapy: allogeneic BMT, acute leukemia
- Open-label, multicentre RCT of standard diagnostic strategy (n=122) vs. galactomannan / PCR (n=118)
- Weekly (OPD) or Biweekly (Inpatient) biomarker testing for 26 weeks
- Biomarker results not released to standard arm physicians

Primary endpoint: Proportion of patients receiving empiric antifungal therapy

Secondary Endpoints: Death (all cause, IA IFI), etc.
Results

- Less empiric antifungal use in the biomarker group, applied to those on fluconazole prophylaxis
- If biomarkers had been available in the standard group, earlier IA diagnosis by a median of 7 days
- 64% in standard diagnosis group would had negative biomarkers
- Biomarker strategy low yield on patients receiving voriconazole or itraconazole
Results

- Biomarker strategy may provide alternative to broad spectrum antifungal prophylaxis.
A Dimorphic Fungus Causing Disseminated Infection in South Africa


- 13 cases identified with an average CD4 was 16
- Skin lesions in all cases; positive blood cultures in approx. 50%
- Dramatic response to antifungal therapy (itraconazole, AmB x 14 d)
- 3/13 died soon after presentation

A New HIV Opportunistic Infection: *Emmonsia pasteuriana*

- Retrospective review of skin biopsy tissue from March 2003 – 2011
- 10/24 cases originally called histoplasmosis were actually due to *Emmonsia sp.*
- 3 more cases found prospectively
A New HIV Opportunistic Infection: *Emmonsia pasteuriana*

- Median age 34
- All patients anemic
- Presented as IRIS in some
- Occasional mucosal ulceration
Dolutegravir: Integrase Inhibitor

- Once daily dosing
- Fixed dose formulation with ABC/3TC to follow
- Higher genetic barrier to resistance than raltegravir
- Compares favourably to raltegravir in treatment-naïve and treatment-experienced populations

Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection

Sharon L. Walmsley, M.D., Antonio Antela, M.D., Ph.D., Nathan Clumeck, M.D., Dan Duiculescu, M.D., Andrea Eberhard, M.D., Felix Gutiérrez, M.D., Laurent Hocqueloux, M.D., Franco Maggiolo, M.D., Uriel Sandkovsky, M.D., Catherine Granier, D.E.S.S., Keith Pappa, Pharm.D., Brian Wynne, M.D., Sherene Min, M.D., and Garrett Nichols, M.D., for the SINGLE Investigators*

Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naïve adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study

Pedro Cahn, Anton L Pozniak, Horacio Mingrone, Andrey Shuklyakov, Carlos Brites, Jaime F Andrade-Villanueva, Gary Richmond, Carlos Beltran Buendia, Jan Fourie, Moti Ramgopal, Debbie Hagins, Franco Felizarta, Jose Madruga, Tanja Reuter, Tamara Newman, Catherine B Small, John Lambard, Beatriz Grinsztejn, David Dorey, Mark Underwood, Sandy Griffith, Sherene Min, on behalf of the extended SAILING Study Team


Lancet 2013; 382: 700–08
Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.

- Congenitally infected infant treated from 30h after birth with VL 19,812 c/mL
- Child lost to follow-up and stopped treatment at 15 months
- No virologic rebound at 23 months, 36 months
- Potential implications for treatment cessation in children, after treatment for primary infection

Towards HIV Eradication

- Treatment at time of acute infection not likely to occur for most

- Can the latent cell reservoir be eliminated?
  - histone deacetylase inhibitors (vorinostat)
  - Gene therapy to interrupt CCR5 receptor expression
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*Lancet 2013; 382: 1525–33*